

Signal Transduction From Membrane Receptors to the Nucleus: MAP Kinases and AP-1

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AP-1 is a chimeric, sequence specific transcriptional activator composed of Jun and Fos subunits. Basal AP-1 activity is present in most cell types prior to their stimulation, but upon exposure to a wide variety of extracellular stimuli it is further induced, resulting in induction of AP-1 target genes. Both physiological and pathological stimuli induce AP-1 activity, which seems to be involved in mitogenesis, differentiation, transformation and inflammation. Both transcriptional and post-transcriptional mechanisms contribute to induction of AP-1 activity. Many of the genes encoding AP-1 components are immediate early genes that are rapidly induced upon cell stimulation. The activity of both newly synthesized and pre-existing AP-1 components is modulated through their post-translational modification. A key role in stimulation of AP-1 activity is played by various mitogen activated protein kinases (MAPKs). The activities of these enzymes are rapidly stimulated in response to various extracellular signals through activation of MAPK modules consisting of a MAPK, a MAPK kinase (MAPKK), and a MAPK kinase kinase (MAPKKK). Upon activation in response to growth factors or phorbol esters, members of the ERK subgroup of MAPKs translocate to the nucleus where they phosphorylate transcription factors, such as TCF/Elk-1, which is bound to the *c-fos* promoter. Phosphorylation of TCF/Elk-1 stimulates its transcriptional activity leading to *c-fos* induction. Increased c-Fos synthesis results in elevated AP-1 activity. Other MAPKs, the JNKs, are activated by growth factors, cytokines and stressors. So far the JNKs have two known nuclear targets, c-Jun and ATF2. These proteins form a heterodimer that binds to a variant AP-1 site within the *c-jun* promoter. Phosphorylation of both c-Jun and ATF2 stimulates their transcriptional activity leading to *c-jun* induction. In addition to induction of c-Jun synthesis, the JNKs contribute to AP-1 activity for phosphorylating of both newly synthesized and pre-existing c-Jun. FRK represents a third subgroup of MAPKs whose activity is stimulated by growth factors but not phorbol esters or stressors. Once activated, FRK phosphorylates c-Fos at a site that enhances its transcriptional activity leading to a further increase in the activity of AP-1 heterodimers containing c-Fos. The molecular organization of the different MAPK molecules involved in AP-1 induction will be discussed, as well as the mechanisms that ensure biological specificity in their action. Briefly, such specificity is obtained at two levels. One is the interaction between the components of each MAPK module and the other is the interaction between MAPKs and their substrates.